c. identifying and/or quantifying a signal resulting from the binding of said transcriptional factor(s) upon said double-stranded DNA sequence(s).

According to M.P.E.P. 2143.03, in order for a claimed invention to be obvious over the prior art, all of the claim limitations must be taught or suggested in the prior art and the prior art must provide motivation to combine the all of the claim limitations to obtain the claimed invention. As discussed in more detail below, Applicant maintains that Peterson does not teach or suggest transcription factor binding sites which are connected to a solid support by a spacer corresponding to or comprising a double-stranded DNA nucleotide sequence of at least 20 base pairs. Furthermore Applicant maintains that Peterson does not teach or suggest the unexpected results obtained by binding the transcription factor to its specific sequence while the specific sequence is connected to the solid support. In addition, Peterson does not teach or suggest linking the transcription factor binding site to an array bearing at least 4 spots/cm^2 of solid support surface, each spot containing double-stranded DNA sequence(s) for the binding of transcriptional factor(s). Because Peterson does not teach or suggest the foregoing, Applicant maintains that Peterson does not render the claimed invention obvious.

The Examiner states that Peterson et al. inherently teach a method where the specific sequence of the double-stranded DNA sequence(s) able to bind with the transcriptional factor is located at a distance of at least 6-8 nm from the surface of the solid support because Peterson et al. use a volume of buffer (blocking and assay) which inherently makes a space of 6-8 nm from the surface of the plate. As recited in amended claim 1, the double stranded DNA sequence comprising a specific sequence recognized by a transcription factor is connected to the solid support by a spacer corresponding to or comprising at least a double-stranded DNA nucleotide sequence of at least 20 base pairs. In contrast, although Peterson et al. allow the components to be mixed in any order, they suggest forming a DNA-protein complex prior to immobilization of the DNA on the solid support (i.e. binding the transcription factor to a binding site which is in solution rather than connected to the surface of a solid support through a spacer. See pages 12-13 and examples). Because Peterson contains no teaching or suggestion of connecting the specific sequence to the solid support by a spacer corresponding to or comprising at least a double-stranded DNA nucleotide sequence of at least 20 base pairs prior to contact with the transcription factor, Applicant maintains that Peterson does not render the claimed invention obvious.

Furthermore, according to M.P.E.P. 2143, objective evidence of unexpected results is relevant to the issue of obviousness. In the present invention, there is an unexpected advantage obtained by connecting the specific sequence to the solid support prior to contacting the specific sequence with the transcription factor. Binding of the double-stranded DNA molecules to the support prior to contacting the DNA with transcription factors results in significantly increased sensitivity relative to methods in which the binding site is contacted with the transcription factor in solution, since the probability of the protein interacting with the DNA is lower in solution than in the case of DNA pre-immobilized on a solid support. In the methods of Peterson et al., both DNAs (free and complexed to the transcription factors) will compete for binding to the support and the higher diffusion rate of the free (smaller) DNA will favor its binding to the support. Thus, the support will be saturated by the free DNA molecules.

In contrast, the method of the present invention allows for more sensitive detection of the transcription factor(s) in comparison with Peterson et al. As stated in the specification as filed on page 24, lines 8-33 and in figure 3 (purified p50), the method according to the present invention allows detection of the transcriptional factor(s) at concentrations of as low as 5×10^{-16} moles/well. According to Peterson et al., the range of transcriptional factor(s) is 10^{-9}M (see examples 1 to 7), equivalent to 10^{-13} moles/well. Thus, the present invention enables detection at a 100-fold lower concentration than those disclosed in Peterson et al. Furthermore, the present invention enables the screening and/or quantification of transcription factors at the concentration in which they exist in cells and cell lysates without requiring purification of the transcription factors. Thus, the unexpected results of detecting a 100-fold lower concentration are achieved by the method of the present invention because the specific sequences recognized by the transcription factor are bound to the support prior to contact with the transcription factor. In view of the foregoing, Applicants maintain that Peterson et al. does not render the claimed invention obvious.

Peterson et al. teach and exemplify a detection method for detecting transcriptional factors in a solution through the use of multi-well plates rather than arrays having at least 4 spots/cm^2 of solid support surface as recited in amended Claim 1. The use of arrays rather multi-well plates allow all assays to be performed on a single surfacer rather than separate multi-well plates. In addition, lower amounts of biological materials are required if the assays are performed on arrays rather than multi-well plates. Finally, the use of arrays rather than multi-well plates allow the analysis of a large number of transcription factors under uniform

binding conditions in contrast to the variability of conditions which may result from using separate multi-well plates. Because there is no teaching or suggestion of using arrays in Peterson, et al., Applicants maintain that Peterson et al. does not render the claimed invention obvious.

For each of the foregoing reasons, Applicants respectfully submit that the claimed invention is not obvious over Peterson et al.

Peterson et al. in view of Voytas et al.

The Examiner has rejected Claim 16 over 35 U.S.C. § 103(a) on the assertion that it would have been obvious to combine the method of Peterson et al. with the HIV integrase transcriptional factor of Voytas et al. (USP 5,976,795, 11/2/99) in order to improve the screening process of transcription factors.

Applicants note that the Examiner stated that one cannot attack nonobviousness by individually attacking the references since the rejection is based upon the combination of references. However, Applicant notes that in order to render the claimed invention obvious the cited combination of references must teach or suggest all of the elements recited in the claims and must provide motivation to combine them to achieve the claimed invention. As noted above, Peterson et al. do not teach or suggest a method in which the specific sequence is connected to the surface of the solid support by a spacer corresponding to or comprising at least a double-stranded DNA nucleotide sequence of at least 20 base pairs, nor does Peterson et al. teach the use of arrays or suggest the increased sensitivity resulting from connecting the specific sequences to the support prior to contact with the transcription factors. Voytas et al. does not teach or suggest a method in which a specific sequence is connected to the surface of the solid support by a spacer, nor does Voytas teach or suggest the use of arrays or the increased sensitivity resulting from connecting the specific sequences to the support prior to contact with the transcription factor. Because the combination of Peterson and Voytas does not teach or suggest all the limitations of the claimed invention and does not provide motivation to combine all the limitations to achieve the claimed invention, the claimed invention is not obvious over the cited references.

In view of the above remarks, Applicants respectfully request withdrawal of the rejections to the claims under 35 U.S.C. § 103(a).

Conclusion

Claim 9 has been canceled without prejudice and claim 1 has been amended. The changes made to the claims by the current amendment, including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. No new matter has been added herewith.

Should any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. **(Twice Amended)** A screening and/or quantification method of one or more transcriptional factors(s) present in a cell or cell lysate, said method comprising the steps of:

a. binding to an insoluble solid support double-stranded DNA sequence(s) at the concentration of at least 0.01 pmole/cm^2 of said solid support surface, wherein the solid support is an array bearing at least 4 spots/cm^2 of solid support surface, each spot containing double-stranded DNA sequence(s) for the binding of transcriptional factor(s), said double-stranded DNA sequence comprising a specific sequence, said specific sequence being able to bind said one or more transcriptional factor(s) and said double-stranded DNA sequence being **[located from]**connected to the surface of the solid support by a spacer corresponding to or comprising at least a double-stranded DNA nucleotide sequence of at least 20 base pairs;

b. putting into contact said one or more transcriptional factor(s) with said bound double-stranded DNA sequence(s); and

c. identifying and/or quantifying a signal resulting from the binding of said transcriptional factor(s) upon said double-stranded DNA sequence(s).